REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

I. CLAIM STATUS & AMENDMENTS

A. Election/Restriction & Claims Under Examination

Claims 1-26 were pending in this application when last examined.

According to the Office Action Summary, claims 1-4, 6-7, and 14 have been examined on the merits, and stand rejected, and claims 5, 8-13, and 15-26 are withdrawn from consideration as being drawn to non-elected subject matter. This summary conflicts with the statement at page 2 of the Office Action which indicates that claims 1-8 and 14 are under examination, including claims 5 and 8 to the extent that they read on the elected species. This statement at page 2 is consistent with the rejections and objections throughout the body of the Action. Also, at page 2 of the Action, claims 10-13 and 15-26 are indicated as withdrawn from consideration.

At page 2, claim 9 is also indicated as withdrawn for being drawn to a non-elected invention. Claim 9 is drawn to a sensor protein comprising the fusion protein comprising a aryl hydrocarbon-alkaline phosphatase hybrid. As discussed below with regard to the scope of enablement rejection, the invention in claim 9 is exemplified in Example 3 of the Specification. Given the scope of enablement rejection, kindly consider examining claim 9 along with the elected invention.

Also, kindly consider examining amended claims 11-14 along with the elected invention, because these claims are now directed to methods of making the sensor protein of claim 1.

B. Claim Amendments

The present amendment amends claims 1, 3-9, 11, 12, and 14 and adds new claims 27 and 28.

The present amendment also cancels claim 2 without prejudice or disclaimer thereto. Applicants reserve the right to file a continuation or divisional application on any canceled subject matter.

Accordingly, claims 1 and 3-28 are pending in this application.

Support for the amendments to claim 1 can be found in the Specification, for example, at page 8, lines 25-29, page 9, lines 23-25, and page 12, lines 12-14.

Support for the amendments to claim 3 can be found in original claim 3 and in the Specification, for example, at page 8, lines 25-29.

Support for the amendments to claims 4-9 can be found in these claims as originally filed.

Support for new claims 27 and 28 can be found in original claims 3 and 6, and in the Specification, for example, at page

Thus, no new matter has been added by this amendment.

II. OBJECTIONS TO THE CLAIMS

Claims 3-5, 8, and 14 are objected to as including non-elected species. Specifically, the Examiner has indicated that the claims will be examined to the extent of the elected species, i.e., hormone receptor for claim 3 and green fluorescent protein for claim 4. See Office Action, page 2, 2nd paragraph.

The foregoing amendments and the following arguments are deemed to overcome the outstanding rejections. Accordingly, pursuant to M.P.E.P. § 820, Applicants respectfully request that a reasonable number of additional non-elected species be examined along with the elected invention. Also, Applicants respectfully request that claims 11, 12, and 14 be retained, since the non-elected method claims 11-13 should be rejoined upon allowance of the product claims.

III. PRIORITY

In item 13, acknowledgment has been made of the claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f). However, the Examiner has incorrectly indicated that certified copies

of the foreign priority documents have not been received. Office Action, page 1, Item 13(c)1; page3, 1st paragraph.

A certified copy of the priority document was submitted along with the Claim of Priority Under 35 U.S.C. § 119 on December 20, 2001.

IV. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-4, 6, and 7 stand rejected under 35 U.S.C. § 112, first paragraph, because the Specification is allegedly not enabling for the full scope of the claims. See Office Action, pages 3-6.

Applicants respectfully traverse this rejection as applied to the amended claims and for the following reasons.

The rejection is unclear as to what is considered enabling. At page 3, lines 13-14, the rejection states that "the specification, while being enabling for a sensor protein comprising an insert-type fusion protein composed of a reporter protein and a binding protein . . . ." However, at page 3, lines 14-17, the rejection further indicates that the Specification is not enabled for all sensor proteins composed of any binding proteins and any receptor proteins and fragments or mutants. Also, at page 4, lines 17-18 of the Office Action, the rejection indicates that the "specification does not provide the information on the structure and function of the claimed fragments and mutants." It appears that the Examiner is concerned with the fragments and mutants language, and that claims directed to a hybrid fusion protein composed of a reporter protein and a binding protein, absent fragments and mutants, are enabled.

The current amendment overcomes this concern with regard to the binding protein by removing the mutant language and by adding the functional limitation that the fragments retain the ability of producing a change in the sensor protein upon binding to a target substance. Also, as for the reporter protein, mutants for the reporter protein are so well known that one of skill in the art can make and use them without undue experimentation.

Nonetheless, at page 5, lines 26-27 of the Action, the rejection implies that the Specification is only enabled for a hybrid composed of the aryl hydrocarbon receptor (Ah) and the

Green Fluorescent Protein (GFP), because the working examples are allegedly drawn to making this one example.

In contrast to this position, the Specification provides working examples of numerous sensor proteins, which exemplify and enable the full scope of the claims.

For instance, Examples 1 and 2 at pages 25, line 20 to page 31, line 10, demonstrates a sensor protein comprising a hybrid composed of β-lactamase (binding protein) and GFP (reporter protein). Figure 5 shows the effectiveness of the GFP-β-lactamase fusion protein.

Example 3, starting at page 31, line 11 (and Figure 6), also demonstrate the effectiveness of a sensor protein comprising a fusion protein hybrid composed of an Ah-alkaline phosphatase. This example is exemplified in claim 9, wherein Ah is the binding protein and alkaline phosphatase is the reporter protein. However, the Examiner withdrew claim 9 as being drawn to a non-elected invention. See Office Action, page 2. Since the Specification clearly enables this species, kindly consider examining claim 9 along with the elected invention.

At page 6, lines 13-14, the Specification also describes a sensor protein comprising a fusion protein formed by inserting calmodulin into the amino acid sequence of a fluorescent protein.

Moreover, the Specification, at page 25, lines 2-19 demonstrates that the insertion of a protein of 100 or more amino acids into GFP does not disrupt the ability of GFP to generate a signal. At page 8, lines 3-9 (and Figure 7), the Specification also demonstrates that a sensor protein can be formed by inserting ***any*** binding protein into a fluorescent reporter protein (claims 4, 6, and 8), such as GFP.

Thus, contrary to the Office's position, the Specification provides numerous working examples demonstrating the effectiveness of the claimed invention. The skilled artisan, upon reading these examples and the teachings in the Specification, would be able to practice the full scope of the claims without undue experimentation.

In addition to these examples, the following three reference articles further demonstrate that the claimed invention is fully enabled: (1) Baird et al., PNAS, vol. 96, pp 11241-11246 (1999), cited by the Examiner; (2) Tucker et al., Nature Biotech., Vol. 19, pp. 1042-1046 (2000),

a copy of which enclosed; and (3) Collinet et al., J. Biol. Chem., vol. 275, no. 23, pp. 17428-17433 (2000), a copy of which is enclosed. These reference articles, all of which were published after Applicants' priority date, disclose the effectiveness of fusion proteins having a similar structure to that of the present invention.

Baird relates to fusion proteins prepared by inserting calmodulin or a zinc finger domain (as the binding protein) into the Tyr-145 of EYFP, ECFP or EGFP (as the reporter protein) of the yellow mutant of GTP. See Baird, page 11241, Abstract. Moreover, as shown at page 11243, left column, lines 32-33, and in Figure 2, Tyr-145 is in the structural loops of the protein. Expression vectors containing a nucleic acid sequence encoding the fusion protein calmodulin/GFP mutant were introduced into cells, and subsequently expressed. This fused protein could be used as an indicator sensor for calcium ion. Baird, page 11244, right column, lines 12-61. Also, it was confirmed that a zinc finger domain/YFP fusion protein could be used as an indicator sensor for Zn^{2+}. Baird, page 11244, right column, line 62 to page 11245, right column.

Tucker relates to a sensor protein comprising a fusion protein composed of an FKBP12 (an estrogen receptor) as the binding protein and DHFR as the reporter protein. Tucker, page 1042, Abstract, and page 1042, right column, Results section, lines 1-17. At page 1042, right column, Results, lines 6-8, Tucker confirms that the activity of the reporter protein, DHFR, is maintained even when the protein is divided by the insertion of the FKBP12 binding protein at amino acid 107 of the DHFR receptor protein.

Similarly, Collinet relates to a fusion protein composed of DHFR (as the binding protein) and PGK (as the reporter protein). As shown in Table 1, on page 17430, DHFR can be inserted into the sites of Asn71, Lys89, Ser129, or Ser290 of PGK. These insertion sites are present on the surface loop regions of the PGK structure which is not directly involved in the catalytic domain. Thus, Collinet demonstrates that two unrelated proteins of more than 150 amino acids can be inserted into a host protein, and both proteins are then able to fold into a functional conformation. Collinet, page 17432, left column, lines 1-7.

These references disclose the effectiveness of fusion proteins that are in similar structure to the fusion protein of the present invention.

Similarly, the instant Specification, at page 12, lines 10-22, also discloses numerous locations/insertion sites on a receptor protein, such as GFP, where a binding protein can be inserted without disrupting the ability of the reporter protein to generate a signal. At page 17, lines 16-20, the Specification teaches that the function of the fusion protein as a sensor can be assessed by detecting a change in a signal generated from the reporter protein upon binding with a target substance. The Specification also provides numerous examples of such sensor proteins as discussed above.

Based on this disclosure, the skilled artisan would be able to extrapolate this information to make a sensor protein comprising an insert-type fusion protein composed of a reporter protein and a binding protein without undue experimentation. Therefore, the Specification is enabling for a sensor protein comprising a fusion protein which comprises a reporter protein and a binding protein.

Furthermore, notwithstanding that the Specification is enabled for the full scope of the claims, new claims 27 and 28 have been added that are directed to the elected species which the Examiner indicate were enabled.

In view of the above, the rejection of claims 1-4, 6, and 7 under 35 U.S.C. § 112, first paragraph, is untenable and should be withdrawn.

V. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-4, 6 and 7 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. See Office Action, pages 6-7.

In view of the foregoing amendments, this rejection is deemed to be overcome.

VI. REJECTION UNDER 35 U.S.C. § 102

Claims 1-4 and 6 are rejected under 35 U.S.C. § 102(a) as anticipated by Baird et al., PNAS, vol. 96, pp 11241-11246 (1999). See Office Action, pages 7-8.

Baird is not available as prior art, because the reference, which has a publication of September 1999, was published after the November 11, 1998 priority date of the instant application. The instant application claims priority under the International Convention to Japanese Patent Application No. 10/320102, filed November 11, 1998. Enclosed is an English translation of this priority document.

In view of the above, the rejection of 1-4 and 6 are rejected under 35 U.S.C. § 102(a) is untenable and should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, the present application is now in condition for allowance and early notice to that effect is hereby requested.

If it is determined that the application is not in condition for allowance, the Examiner is invited to telephone the undersigned attorney at the number below to expedite prosecution of the present application.

Respectfully submitted,

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ATTACHMENT TO AMENDMENT AND REPLY:

1. Tucker et al., Nature Biotech., Vol. 19, pp. 1042-1046 (2000);

2. Collinet et al., J. Biol. Chem., vol. 275, no. 23, pp. 17428-17433 (2000);

3. English translation of priority document, Japanese Patent Application No. 10/320102, filed November 11, 1998.